

Solvation descriptors for ferrocene, and the estimation of some physicochemical and biochemical properties

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Literature data on the solubility of ferrocene in nonaqueous solvents have been combined with the aqueous solubility to give partition coefficients from water to solvents, and have also been combined with the vapour pressure at 298 K to give gas–solvent partition coefficients. These two sets of partitions have been analysed through the solvation equations of Abraham to yield values of the solvation descriptors. Ferrocene is shown to have about the same dipolarity/polarisability and hydrogen bond basicity as naphthalene. From the solvation descriptors, various properties of ferrocene have been estimated, including the lipophilicity, the blood–brain distribution, and the vapour toxicity (as the nasal pungency threshold).

Paramètres de solvation du ferrocène et estimation de diverses propriétés physico-chimiques et biologiques. Les valeurs de solubilité du ferrocène dans l'eau et divers solvants organiques, tirées de la littérature, ont été utilisées afin d'obtenir les valeurs de $\log P$ exprimant le partage du ferrocène entre l'eau et chacun des solvants étudiés. De la même façon, les coefficients de partage entre phase gazeuse et phase condensée, $\log L^S$, ont été calculés à partir de la pression de vapeur du ferrocène à 298 K et des valeurs de solubilité du ferrocène dans divers solvants. Ces valeurs de $\log P$ et $\log L^S$ ont été utilisées à travers les équations de solvation d'Abraham permettant ainsi l'obtention des paramètres de solvation du ferrocène. Le composé ferrocène semble avoir la même dipolarité, polarisabilité et basicité de liaison hydrogène que la naphthalène. Les paramètres de solvation ont également permis l'estimation de certaines propriétés du ferrocène telles que sa lipophilicité, sa capacité de distribution entre le sang et le cerveau et sa toxicité de vapeur comme le seuil d'irritation nasale.

A number of physicochemical properties of ferrocene at 298 K are known; these include the vapour pressure,^{1–7} the enthalpy of sublimation,⁸ the solubility in water, as $\log S_w$ (-4.47 ,⁹ -4.37 ,¹⁰ -4.30 ,¹¹ and -4.17),¹² the Henry's constant in water (1.34×10^6 Pa) or the equivalent Ostwald solubility coefficient (102),¹⁰ and various electrochemical properties¹¹ mostly relevant to the ferrocene/ferrocenium couple.

The 1 : 1 hydrogen bond basicity, β_2^H , is known¹³ to be 0.27, which is rather more than that for cyclohexa-1,4-diene (0.11),¹⁴ but almost the same as that for hexamethylbenzene (0.26¹³ or 0.24¹⁴); the value of β_2^H for cyclopentadiene seems not to be known. A determination of the complexation of ferrocene with phenol in tetrachloromethane¹⁵ yields (*cf.* ref. 13) a value of 0.20 for β_2^H of ferrocene, if the observed complexation constant at 302 K is taken as an estimate of that at 298 K. This value of 0.20 is in reasonable agreement with the listed value of 0.27 (see above).

However, in order to analyse solubility-related properties, it is not the 1 : 1 hydrogen bond basicity that is relevant, but the corresponding basicity when the solute is surrounded by solvent molecules, that is,¹⁶ the overall, or summation, hydrogen bond basicity. It is the aim of the present work to determine the solvation parameters for ferrocene, including the overall, or summation, hydrogen bond basicity, and to show how these parameters may be used to deduce various physicochemical properties.

Methodology

We start with the set of equations we have constructed¹⁶ for the partition of solutes between water and a given solvent, using our general solvation equation, eqn. (1), with a more simplified notation than originally given.¹⁶

$$\log P = c + eE + sS + aA + bB + vV \quad (1)$$

In eqn. (1), the dependent variable is $\log P$, the partition coefficient of a series of solutes between water and a given solvent. The independent variables are as follows, with the original¹⁶ notation in parentheses: $E(R_2)$ is the solute excess molar refractivity in units of $(\text{cm}^3 \text{ mol}^{-1})/10$, $S(\pi_2^H)$ is the solute dipolarity/polarisability, $A(\sum \alpha_2^H)$ and $B(\sum \beta_2^H)$ are the overall, or summation, hydrogen bond acidity and basicity, respectively and $V(V_x)$ is the McGowan characteristic volume¹⁷ with units of $(\text{cm}^3 \text{ mol}^{-1})/100$. Table 1 gives the coefficients in eqn. (1) for the water–solvent partitions we shall consider.^{18–24} Note that many of these are 'hypothetical partitions' between pure water and the pure dry solvent; these are shown as 'dry' in Table 1. Although 'hypothetical', these partitions are very useful; as we show later, they can be used to predict solubilities in the pure dry solvent.

The partition coefficient of a solid between water and a solvent phase can be obtained from the solubility of the solid in water, S_w , and the solvent, S , [eqn. (2)], provided that the

Table 1 Coefficients in eqn. (1) for partition between water and solvents^a

Solvent	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>
n-Hexane	0.361	0.579	−1.723	−3.599	−4.764	4.344
n-Heptane	0.325	0.670	−2.061	−3.317	−4.733	4.543
n-Octane	0.223	0.642	−1.647	−3.480	−5.067	4.526
2,2,4-Trimethylpentane	0.288	0.382	−1.668	−3.639	−5.000	4.561
Cyclohexane	0.159	0.784	−1.678	−3.740	−4.929	4.577
Chloroform	0.327	0.157	−0.391	−3.191	−3.437	4.191
Tetrachloromethane	0.260	0.573	−1.254	−3.558	−4.588	4.589
Benzene	0.142	0.464	−0.588	−3.099	−4.625	4.491
Toluene	0.143	0.527	−0.720	−3.010	−4.824	4.545
Carbon disulfide	0.047	0.686	−0.943	−3.603	−5.818	4.921
Propanone, dry	0.335	0.349	−0.231	−0.411	−4.793	3.963
Acetonitrile, dry	0.413	0.077	0.326	−1.566	−4.391	3.364
Methanol, dry	0.329	0.299	−0.671	0.080	−3.389	3.512
Ethanol, dry	0.208	0.409	−0.959	0.186	−3.645	3.928
Butan-1-ol, dry	0.153	0.438	−1.177	0.096	−3.919	4.122
Propan-2-ol, dry	0.063	0.320	−1.024	0.445	−3.829	4.067
Ethylene glycol, dry	−0.313	0.419	−0.409	0.906	−2.558	2.771
Octan-1-ol, wet	0.088	0.562	−1.054	0.034	−3.460	3.814

^a The solvents denoted as ‘dry’ are those for which partitions refer to transfer from water to the pure dry solvent. The other partitions are from water (more correctly water saturated with solvent) to the solvent saturated with water (see text).

same solid phase is in equilibrium with the saturated solutions in water and in the given solvent.²⁵

$$\log P = \log S - \log S_w \quad (2)$$

We can therefore use the solubility of ferrocene in water, $\log S_w = -4.47$,⁹ together with available solubilities in a variety of nonaqueous solvents,^{9,26–32} to deduce $\log P$ values for the partition of ferrocene from water to the solvents. These are given in Table 2. Note that if we had used the $\log S_w$ value of Wu *et al.*,¹⁰ our calculations would have been almost identical.

For partition of solutes between the gas phase and solvents, eqn. (3) is used¹⁶ instead of eqn. (1). The dependent variable is now $\log L^S$, where L^S is the gas–solvent partition coefficient, or Ostwald solubility coefficient, for a series of solutes in a given solvent, defined as shown in eqn. (4).

$$\log L^S = c + eE + sS + aA + bB + lL \quad (3)$$

$$L^S = \frac{[\text{conc. of solute in solvent}]}{[\text{conc. of solute in gas phase}]} \quad (4)$$

The descriptors in eqn. (3) are the same as those in eqn. (1), except that V is replaced by L ($\log L^{16}$ where L^{16} is the gas–liquid partition coefficient on hexadecane at 298 K).³³ Values of $\log L^S$ for ferrocene in solvents can be obtained from the saturated vapour concentration of ferrocene at 298 K and the solubility in a given solvent, through eqn. (4), and are also given by eqn. (5), where L^W is the Ostwald solubility coefficient of ferrocene in water.

$$\log L^S = \log L^W + \log P \quad (5)$$

Ribeiro da Silva and Monte⁷ list eleven values of the saturated vapour pressure of ferrocene at 298 K, ranging from 0.858 to 1.16 Pa. We chose an intermediate value of 1.00 Pa, corresponding to a vapour concentration (C_G in $\text{dm}^3 \text{mol}^{-1}$), of $\log C_G = -6.39$ which, combined with $\log S_w = -4.47$, leads to a value of 1.92 for $\log L^W$. The values of $\log L^S$ for ferrocene in various solvents are shown in Table 2, and the coefficients in eqn. (3) for a number of solvents are collected in Table 3.

A key descriptor is the McGowan volume that is obtained from atomic and bond contributions,¹⁷ the former from atomic parachors.³⁴ For a number of elements, McGowan³⁴ calculated atomic parachors for the atom in two electronic states, thus leading to two different atomic volumes. For iron, the two atomic volumes are 0.4015 and 0.0581 in our usual units of $(\text{cm}^3 \text{mol}^{-1})/100$. However, it seems clear from examples quoted by McGowan that transition metals have variable atomic volumes. Thus, Fe in $\text{Fe}(\text{CO})_5$ has³⁴ an atomic volume of 0.284, intermediate between the two above volumes. We have shown previously²⁴ that values of V are well correlated with liquid molar volumes at 298 K, V_{liq} . For a series of cyclic compounds, the regression equation is:

$$V = -0.0882 + 0.8837V_{\text{liq}} \quad (6)$$

$$n = 20, \text{sd} = 0.0428, r^2 = 0.988, F = 1534$$

with both volumes in $(\text{cm}^3 \text{mol}^{-1})/100$. Here, n is the number of data points, sd is the standard deviation, r^2 is the variance

Table 2 Solubilities of ferrocene, (S in mol dm^{-3}), and derived partition coefficients

Solvent	$\log S$	$\log P$	$\log L^S$	Ref. ($\log S$)
n-Hexane	−0.818	3.652	5.576	26,31,32
n-Heptane	−0.781	3.689	5.613	26–28,32
n-Octane	−0.846	3.624	5.548	32
n-Dodecane	−0.823	3.646	5.570	29
2,2,4-Trimethylpentane	−0.860	3.610	5.534	27
Cyclohexane	−0.513	3.957	5.881	26–28,32
Chloroform	0.372	4.842	6.766	31 (not used)
Tetrachloromethane	−0.159	4.311	6.235	27
Benzene	−0.031	4.439	6.363	26,28,31,32
Toluene	−0.030	4.440	6.364	26,32
Carbon disulfide	0.012	4.482	6.406	27
Propanone	−0.509	3.961	5.885	31
Acetonitrile	−0.790	3.680	5.604	9
Methanol	−1.050	3.420	5.344	9
Ethanol	−1.096	3.374	5.298	26
Butan-1-ol	−1.034	3.436	5.360	26
Propan-2-ol	−1.048	3.422	5.346	31
Ethylene glycol	−1.928	2.542	4.466	30
Water	−4.47		1.924	9
Hex-1-ene	−0.303	4.167	6.091	32 (not used)
Pyridine	−0.080	4.390	6.314	9 (not used)
1,4-Dioxane	−0.116	4.354	6.278	27 (not used)
Dimethyl sulfoxide	−0.69	3.780	5.704	9 (not used)

Table 3 Coefficients in eqn. (3) for partition between the gas phase and solvents^a

Solvent	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>l</i>
n-Hexane	0.292	−0.169	0.000	0.000	0.000	0.979
n-Heptane	0.275	−0.162	0.000	0.000	0.000	0.983
n-Octane	0.215	−0.049	0.000	0.000	0.000	0.967
2,2,4-Trimethylpentane	0.275	−0.244	0.000	0.000	0.000	0.972
Cyclohexane	0.163	−0.110	0.000	0.000	0.000	1.013
Chloroform	0.116	−0.467	1.203	0.138	1.432	0.994
Tetrachloromethane	0.282	−0.303	0.460	0.000	0.000	1.047
Benzene	0.107	−0.313	1.053	0.457	0.169	1.020
Toluene	0.121	−0.222	0.938	0.467	0.099	1.012
Carbon disulfide	0.101	0.251	0.177	0.027	0.095	1.068
Propanone, dry	0.154	−0.277	1.522	3.258	0.078	0.863
Acetonitrile, dry	−0.007	−0.595	2.461	2.085	0.418	0.738
Methanol, dry	−0.004	−0.215	1.173	3.701	1.432	0.769
Ethanol, dry	0.012	−0.206	0.789	3.635	1.311	0.853
Butan-1-ol, dry	−0.039	−0.276	0.539	3.781	0.995	0.934
Propan-2-ol, dry	−0.060	−0.335	0.702	4.017	1.040	0.893
Ethylene glycol, dry	−0.937	0.215	1.511	4.651	2.591	0.571
Octan-1-ol, wet	−0.198	0.002	0.709	3.519	1.429	0.858

^a The solvents denoted as ‘dry’ are those for which partitions refer to transfer from the gas phase to the pure dry solvent. The other partitions are from the gas phase to the solvent saturated with water (see text).

and *F* is the *F*-statistic. There are a number of ferrocene derivatives that are liquid at 298 K, and for which *V*_{liq} is then available (see Table 4). From the ethyl and n-butyl derivatives we can estimate *V*_{liq} for ferrocene itself to be 1.342 at 298 K. Then, from eqn. (6), it is possible to estimate the corresponding values of *V*. These can be compared with the calculated *V* values, using the atomic contribution of 0.0581 for Fe. As shown in Table 4, the agreement is very good, and we can use this atomic contribution to calculate *V* for ferrocene to be 1.1209 in units of (cm³ mol^{−1})/100. A value of 1.354 for *E* for ferrocene can be estimated from those for ethylferrocene and n-butylferrocene. It must be said, however, that the agreement between the volumes shown in Table 4 might be fortuitous. We therefore suggest that in the case of transition metals, it is much safer to assign the atomic contribution through an equation such as eqn. (6), if at all possible.

Once values of *E* and *V* are available, the remaining four descriptors in eqn. (1) and eqn. (3) can be obtained, as we have described previously.^{24,25,35,36} In brief, we have values of log *P* and log *L*^S for ferrocene, derived from measured values of log *S*, as shown in Table 2, and we have the coefficients already determined for the corresponding equations, using eqn. (1) and eqn. (3) (see Tables 1 and 3). The only unknowns are the descriptors *S*, *A*, *B* and *L*, and these can be assigned by a least-squares procedure that minimises the observed and calculated values of log *P* and log *L*^S. We have 19 equations in log *P* and 19 equations in log *L*^S, so that our analysis covers quite a range of solvents. The log *P* and log *L*^S values for chloroform solvent were somewhat anomalous and were omitted. The best-fit solution of the remaining 36 equations yielded the following values: *S* (0.85), *A* (0.00), *B* (0.20) and *L*

(5.6244). How well these descriptors, together with *E* = 1.354 and *V* = 1.1209, reproduce the log *P*, log *L*^S and original log *S* values is shown in Table 5. The log *S* values can be calculated in two ways: (i) log *S*(calc) = log *P*(calc) + log *S*_w, and (ii) log *S*(calc) = log *L*^S(calc) + log *C*_G. Table 5 summarises the results of the calculations.

The log *P* values are correlated with sd = 0.098, the log *L*^S values with sd = 0.101, and the total 36 values with sd = 0.098 log units. The original log *S* values in the nonaqueous solvents (17 in number, if chloroform is excluded) are reproduced with sd values of 0.101 [method (i)] and 0.105 [method (ii)], average absolute deviations of 0.075 and 0.082, and average deviations of −0.008 and 0.004, respectively. The general method, based on eqn. (1) and eqn. (3), is therefore capable of correlating the original log *S* values very well, and could be used to predict further log *S* values in solvents for which we have the coefficients in eqn. (1) or eqn. (3), to within about 0.1 log units. This is one particular use of ‘hypothetical’ water–dry solvent partitions. In addition, the method provides solvation descriptors for ferrocene that can be used to compare chemical properties with those of other relevant compounds.

In Table 6 are values of the solvation descriptors in eqn. (1) and eqn. (3) for ferrocene, and for a number of other related compounds, all of which have zero hydrogen bond acidity. The *E* and *S* descriptors are in no way anomalous, and are both slightly more than those calculated for two cyclopentadienyl rings. The overall hydrogen bond basicity (*B*), at 0.20, is interesting in that it is only slightly smaller than that of two cyclopentadienyl rings (2 × 0.12) (see Table 6) so that the Fe atom has only a very small effect on the availability of electron pairs for hydrogen bonding. This is also the case for the 1 : 1 hydrogen bond parameter β₂^H, obtained by a completely different method. The *L* parameter (5.622), which is related to solute size, is substantially larger than that calculated for two cyclopentadienyl rings (4.444). This is as expected, since the Fe atom must contribute to any size-related property.

Once the solvation descriptors are available for ferrocene, it is possible to calculate a number of physicochemical and biological properties, using the general equations eqn. (1) and eqn. (3); some of these properties are collected in Table 7. Various water–solvent partition coefficients can be calculated, of which the most important is the water–octanol partition, used as an indicator of solute lipophilicity.³⁷ The coefficients in eqn. (3) for this practical partition are given in Table 3, and

Table 4 Liquid molar volumes, estimated McGowan volumes, through eqn. (6), and calculated McGowan volumes with *V* = 0.0581 for Fe, all in (cm³ mol^{−1})/100

Compound	<i>V</i> _{liq}	<i>V</i> [eqn. (6)]	<i>V</i> (calc.)	<i>E</i>
Dimethylaminoferrocene	1.98	1.661	1.6434	1.417
n-Butylferrocene	2.066	1.737	1.6845	1.337
Ethylferrocene	1.704	1.417	1.4027	1.358
Ferrocene	1.342 ^a	1.097	1.1209	1.354

^a Estimated from the ethyl and n-butyl derivatives.

Table 5 Observed and calculated values of log *S*, log *P* and log *L^S* for ferrocene

Solvent	log <i>S</i> obs.	log <i>P</i> obs.	log <i>L^S</i> obs.	log <i>S</i> calc. ^a	log <i>S</i> calc. ^b	log <i>P</i> calc.	log <i>L^S</i> calc.
n-Hexane	−0.818	3.652	5.576	−0.873	−0.825	3.597	5.569
n-Heptane	−0.781	3.689	5.613	−0.844	−0.810	3.626	5.584
n-Octane	−0.846	3.624	5.548	−0.718	−0.807	3.752	5.587
n-Dodecane	−0.823	3.646	5.570	−0.859	−0.770	3.611	5.624
2,2,4-Trimethylpentane	−0.860	3.610	5.534	−0.970	−0.982	3.500	5.412
Cyclohexane	−0.513	3.957	5.881	−0.531	−0.682	3.939	5.712
Chloroform	0.372	4.842	6.766	(−0.252)	(−0.011)	4.218	6.383
Tetrachloromethane	−0.159	4.311	6.235	−0.274	−0.269	4.196	6.152
Benzene	−0.031	4.439	6.363	−0.091	−0.045	4.379	6.349
Toluene	−0.030	4.440	6.364	−0.096	−0.065	4.374	6.329
Carbon disulfide	0.012	4.482	6.406	0.057	0.223	4.527	6.617
Propanone	−0.509	3.961	5.885	−0.375	−0.452	4.095	5.942
Acetonitrile	−0.790	3.680	5.604	−0.783	−0.880	3.687	5.514
Methanol	−1.050	3.420	5.344	−1.048	−1.080	3.422	5.314
Ethanol	−1.096	3.374	5.298	−0.849	−0.930	3.621	5.464
Butan-1-ol	−1.034	3.436	5.360	−0.889	−0.894	3.581	5.500
Propan-2-ol	−1.048	3.422	5.346	−1.050	−1.080	3.420	5.314
Ethylene glycol	−1.928	2.542	4.466	−1.969	−2.026	2.501	4.368
Water	−4.470		1.924				1.938
Water	−4.470		1.924			1.948	
Hex-1-ene	−0.303	4.167	6.091			N/A	
Pyridine	−0.080	4.390	6.314			N/A	
1,4-Dioxane	−0.116	4.354	6.278			N/A	
Dimethyl sulfoxide	−0.690	3.780	5.704			N/A	

^a Method (i), see text. ^b Method (ii), see text.**Table 6** Comparisons of some properties of ferrocene

Compound ^a	<i>E</i>	<i>S</i>	<i>B</i>	<i>V</i>	<i>L</i>	β_2^H ^b	log <i>P_{oct}</i>
Ferrocene	1.35	0.85	0.20	1.121	5.622	0.20/0.27	3.54 ^c
Benzene	0.61	0.52	0.14	0.716	2.786	0.15/0.15	2.13
Biphenyl	1.36	0.99	0.26	1.324	6.014	0.20/0.20	4.01
Naphthalene	1.34	0.92	0.20	1.085	5.161	0.21/0.21	3.30
Cyclopentadiene	0.42	0.35	0.12	0.618	2.222		1.89 ^d
1,3-Cyclooctadiene	0.60	0.35	0.14	1.041		0.13/0.13	
Butanone	0.17	0.7	0.51	0.688	2.287	0.48	0.29
Dimethylformamide	0.37	1.31	0.74	0.647	3.173	0.66	−1.01

^a All listed compounds have a zero value for *A*. ^b Ref. 13 and 15. ^c Observed values are 2.66 (ref. 38) and 3.46 (ref. 39), see text. ^d Calculated *C* log *P* value, ref. 38.

lead to a predicted value of 3.54 for log *P_{oct}*. However, the most recent issue of the MedChem data base³⁸ lists an unpublished measured value of 2.66 for log *P_{oct}*, which would imply that our calculations are in error. We were fortunate that Dr Bryan Slater offered to re-measure log *P_{oct}*; the new measured value is 3.46 ± 0.03 as an average of three separate determinations.³⁹ Our predicted value of 3.54 is in excellent agreement with the measured value, and so we have some confidence in our ability to predict properties of ferrocene.

Some comparisons of lipophilicity are in Table 6; ferrocene is rather strongly lipophilic, of the same order as aromatic compounds with two rings, such as biphenyl and naphthalene.

Table 7 The predictions for some properties of ferrocene

Property	Details	Value
Lipophilicity	log <i>P_{oct}</i>	3.54
Δ log <i>P_{eye}</i>	Δ log <i>P</i>	−0.45
Blood–brain distribution	log <i>BB</i>	0.64
Skin permeation	log <i>kp</i> /cm s ^{−1}	−3.40
Nasal pungency threshold	NPT/ppm	37

Another well-known descriptor that is often used in quantitative structure–activity relationships is the Δ log *P* parameter of Seiler,⁴⁰ defined as:

$$\Delta \log P = \log P_{\text{oct}} - \log P_{\text{eye}} \quad (7)$$

where *P_{eye}* is the water–cyclohexane partition coefficient. Our calculated negative value (−0.45) for Δ log *P* is as expected^{18,41} for a solute with zero hydrogen bond acidity. The blood–brain distribution of ferrocene can be estimated⁴² to be 0.64, putting it near the middle of the observed range (−2.2 to +1.4).⁴³ On the other hand, our calculated value for permeation from water through human skin,⁴⁴ log *kp* = −3.4 with *kp* in units of cm s^{−1}, would make ferrocene one of the most penetrative compounds known.⁴⁴ Properties of gaseous ferrocene can be estimated through eqn. (3); for example, the nasal pungency threshold, an indicator of the toxicity of vapours, can be estimated through our previously published equation⁴⁵ as 37 ppm. In comparison to a very poorly potent vapour, methyl acetate, with a measured threshold of 1.1×10^5 ppm and a very potent vapour, dodecyl acetate, with a measured threshold of 1.3 ppm, ferrocene is potentially quite potent. However, the very low vapour pressure of ferrocene (1.00 Pa at 298 K) corresponds to a vapour concentra-

tion of only 9.9 ppm, so that the threshold concentration will not be reached.

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